183. The method of **Claim 165**, wherein the GLP-1 analog has an arginine substituted for lysine at position 34.

Remarks

On December 12, 2001 and on January 3, 2002, telephonic interviews were held between Gregory A. Cox and Examiner David Lukton. The Examiner is thanked for granting the interviews and for his helpful comments. During the interviews, data that further supports the utility of the claimed invention was discussed. Applicants have provided the data in the form of a declaration and discuss the data below.

In this response, Applicants have canceled all claims and submit new independent Claim 122 directed to a method of normalizing blood glucose by administering to the lungs a GLP-1 molecule selected from an intermediate genus of GLP-1 analogs and derivatives, wherein the GLP-1 analogs and derivatives are protected from the activity of dipetidyl peptidase IV (DPP IV). Support for this claim can be found throughout the specification and in particular from page 9, line 26 to page 10, line 2 and on page 5, lines 4 to 8. Applicants also submit new dependent Claims 144 to 148 directed to specified GLP-1 analogs and derivatives useful in the claimed method of normalizing blood glucose by pulmonary administration. Support for these claims can be found throughout the specification and in particular from page 7, line 3 to page 11 line 30. Applicants also submit new dependent Claims 165 to 167 directed to specified GLP-1 derivatives that are prepared by the process of acylating GLP-1 analogs. Support for these claims can be found throughout the specification and in particular from page 7, line 12 to page 9 line 25.

REJECTION UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner rejected Claims 70-121 under 35 U.S.C. §112 first paragraph as containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Although the Examiner stated that Applicants have shown Val^8-GLP-1 can be administered to the lungs, and that certain antigenic determinants of the peptide appear in the serum, the Examiner argues that Applicant's immunoassay does not establish that intact peptide appears in serum and that there is no evidence that the peptide is 'useful' when delivered by pulmonary means. The Examiner suggested that because proteases are quite abundant in lung tissue, degradation is a significant problem in pulmonary administration of peptides. Even though some other peptides have been successfully delivered by pulmonary means, the Examiner noted that there have been sufficient failures such that whether untested peptides can be delivered pulmonarily is unpredictable.

Applicants respectfully request reconsideration and withdrawal of the rejection. Applicants have demonstrated that Val^8-GLP-1, which is representative of a class of DPP IV protected analogs, can be successfully absorbed into the serum when administered by pulmonary means as evidenced in the examples. (For example see p. 33 of Applicants' specification). These data alone are sufficient to establish the enablement and usefulness of the claimed invention.

However, to advance prosecution, Applicants submit pharmacodynamic data showing that a dry powder formulation of Val^8-GLP-1(7-37)OH, which is representative of DPP IV protected GLP-1 molecules, administered by pulmonary means to dogs decreased plasma glucose compared to sham air exposure without the GLP-1 molecule. This data is consistent and

corroborate the teachings in the specification that GLP-1 molecules administered to the lung and detected in the serum are biologically active and useful. Therefore, the rejection is now moot.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

The Examiner rejected Claims 70-121 under 35 U.S.C. §112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 70-121 were rejected for reciting the term "effective dose," rendering the claims indefinite "as to the objective(s) of efficacy." The Examiner also rejected the claims as being indefinite as to the endpoint and process steps. The Applicants define effective dose in the specification. "GLP-1 related compounds described above are administered by inhalation in a dose effective manner to introduce circulating therapeutic levels which results in reducing abnormally high blood glucose levels." (See p. 12 line 30 to p.13 line 15). Further, the MPEP addresses this issue and states that the phrase "effective amount" is definite when read in light of the supporting disclosure. (MPEP § 2173.05(c)). Based on Applicants' specification, the ordinary skilled person would understand that effective dose means to administer enough DPP IV protected GLP-1 molecule to the lungs of a patient such that therapeutic levels of the GLP-1 molecule will be absorbed into the circulation and have the effect of normalizing blood glucose.

The Examiner suggested that Applicants employ the language "for a time and under conditions effective to detect the presence of said peptide in the serum of a patient" to overcome these rejections. Applicants do not believe that Examiner's proposed language adds further definiteness to the

claim or is a further limitation to the claim. This is form over substance. However, to further prosecution, Applicants have offered "normalizing blood glucose" language in the amended claims as a measure to define "effective dose." Normalization of blood glucose will occur after a period of time and under conditions when the peptide is circulating at therapeutic levels in the serum of a patient.

Various claims (e.g., 81, 88, and 95) were rejected for reciting the phrase "less than about" or "at least about" thus rendering the claims indefinite. Applicants continue to disagree with the merits of this rejection. The MPEP addresses this issue and suggests that these types of phrases are definite when read in light of the supporting disclosure (MPEP § 2173.05(b)(A)). Applicants' specification is clear regarding the meaning of the terms. The Examiner suggested that Applicants delete the term "about" from the claims and add another claim which recites just the "about" language. The Examiner suggested that this type of amendment would in no way further limit the claims. To further prosecution, Applicants have amended the claims as the Examiner suggested. This rejection is now moot.

The Examiner pointed out that "[s]everal [dependent] claims, e.g., 77 and 84 recite that the GLP-1 is <u>not</u> administered by itself, but instead is administered in combination with a carrier so as to form a 'pharmaceutical composition.'" Applicants have amended the dependent claims to be consistent with the independent claim, thus rendering the objection moot.

REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected Claims 70-121 under 35 U.S.C. §103 as being unpatentable over Drucker (USP 5846937) in view of Galloway (USP 5705483); or Smith (USP 5908830) in view of

Galloway; or Knudsen (WO 98/20895) in view of Galloway; or Gelfand (EP 0619322) in view of Galloway; or Kirk (WO 93/18785) in view of Galloway. The Examiner states that the Drucker, Smith, Knudsen, or Gelfand reference teach administration of GLP peptides by pulmonary means and the Kirk reference teaches nasal administration of GLP peptides, while Galloway teaches that Val^8-GLP-1 resists the proteolytic action of DPP-IV. The Examiner concludes that it would have been obvious to one of ordinary skill to administer Val^8-GLP-1 to a patient by pulmonary means. Applicants request reconsideration and withdrawal of the rejection.

The Examiner appears to be selectively using the prior art to support an obviousness rejection, while not considering it to be skill of the art when making an enablement rejection. The Federal Circuit has commented negatively on the inconsistency of arguing on the one hand that prior art in combination taught a skilled person how to make and use an invention, and on the other hand arguing that this prior art plus Applicant's specification did not adequately enable a skilled person to make and use the invention. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The Examiner has twice rejected Applicants' application for not enabling the claimed invention arguing there is no evidence that intact and active GLP-1 peptides appear in the serum after pulmonary administration. Likewise, the Examiner has twice rejected Applicants' application for being obvious over the cited art. This is the same inconsistency that the Federal Circuit rejected in *Hybritech*.

The cited references (Drucker, Smith, Knudsen, Gelfand, or Kirk) either by themselves or with the Galloway reference do not establish a reasonable likelihood that any GLP-1 peptide could be expected to be administered by pulmonary means. The Examiner stated that pulmonary administration of peptides is difficult and that there are proteases in the lung

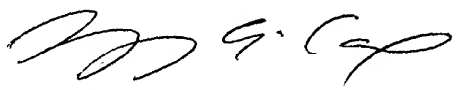
that can degrade peptides. The Examiner suggested that whether an untested peptide can be successfully delivered pulmonarily is unpredictable. In the final rejection on page 8, the Examiner stated, "Applicants have also argued that references do not prove that intact, unhydrolyzed peptides can be administered to the bloodstream. Applicants are correct on this point. But applicants have also not shown this to be the case." Therefore, the Examiner's acknowledgment that the art does not explicitly or implicitly teach or provide a reasonable expectation of success that the GLP-1 molecules can be administered by pulmonary means necessitates the conclusion that the claimed invention is unobvious. In fact the cited references do not even focus on or contain any experimental details regarding administration of GLP-1 molecules by pulmonary means, but to the extent administration of GLP-1 molecules is disclosed at all, they merely contain generic boilerplate type statements regarding various routes of administration. The references lack an expectation of success and, therefore, cannot support an obviousness rejection.

Furthermore, there is no motivation to combine the cited references (Drucker, Smith, Knudsen, Gelfand, or Kirk) with the Galloway reference to produce the teachings in the claimed invention. Motivation is a factual question that cannot be resolved on "subjective belief and unknown authority." *In re Lee*, 2002 U.S. App. LEXIS 855, at *12 (Fed. Cir. 2002). "It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher.'" *Id.* (quoting *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)). Thus, without using Applicant's specification, there is no teaching, or motivation to combine the references and arrive at the successful pulmonary administered of the GLP-1 molecules.

SUMMARY AND CONCLUSION

In conclusion, in view of the remarks provided herein above, it is respectfully submitted that Applicants have enabled their invention. The Applicants provide further support for the claimed invention with the accompanying pharmacodynamic data showing a biologically active GLP-1 molecule administered by pulmonary means. The claims are definite and particularly point out and distinctly claim the subject matter being sought. The Examiner's case of obviousness cannot be maintained. Without using Applicant's specification, there is no teaching, or motivation that a GLP-1 peptide can be successfully administered by pulmonary means. Reconsideration and withdrawal of the rejections are therefore requested.

Respectfully submitted,



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February 1, 2002